PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 271/06, 277/10, 277/12, 233/28, 263/16, A61K 31/41, 31/425, 31/415, 31/42 — A1

(11) International Publication Number: **WO 98/38177**

(43) International Publication Date: 3 September 1998 (03.09.98)

(21) International Application Number: PCT/US98/03373

(22) International Filing Date: 27 February 1998 (27.02.98)

(30) Priority Data:
08/808,263 28 February 1997 (28.02.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 08/808,263 (CON)
Filed on 28 February 1997 (28.02.97)

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: HETEROCYCLIC COMPOUNDS AND THEIR USE FOR INHIBITING β–AMYLOID PEPTIDE

(57) Abstract

Disclosed are compounds which inhibit β–amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease. Also disclosed are pharmaceutical compositions comprising a compound which inhibits β–amyloid peptide release and/or its synthesis as well as methods for treating Alzheimer's disease both prophylactically and therapeutically with such pharmaceutical compositions.

(S)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate was free based by partitioning between methylene chloride and 1M potassium carbonate. The free amine was then coupled with N-Boc-alanine following General Procedure III-D.

$C_{24}H_{28}N_4O_4$ (MW = 436.56); mass spectroscopy 436.

Anal. Calc. for $C_{24}H_{28}N_4O_4$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.79; H, 6.68; N, 12.80.

Step C - Preparation of 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(tert-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one, the title compound was prepared as a white foam.

Anal. Calc. for $C_{19}H_{19}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 70.11; H, 6.85; N, 15.01.

Example 8-C

Synthesis of 3-(L-Alaninyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

A solution of 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-5-phenyl-1H-1,4-Benzodiazepin-2-one (1 eq; Neosystem) in DMF was cooled to 0°C and treated with potassium *tert*-butoxide (1 eq; 1.0M solution in THF). The resultant yellow solution was stirred at 0°C for 30 minutes then quenched with methyl iodide (1.3 eq). After stirring an addition 25 minutes the reaction was diluted with methylene chloride and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified via HPLC chromatography eluting with a gradient of 20→30% ethyl acetate/hexanes.

$C_{24}H_{20}ClN_3O_3$ (MW = 433.92); mass spectroscopy 433.

Anal. calcd for $C_{24}H_{20}ClN_3O_3$: C, 66.44; H, 4.65; N, 9.68. Found: C, 66.16; H, 4.50; N, 9.46.

Step B - Preparation of 3-Amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

Step C - Preparation of 3-[N'-tert-Butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure III-D using N-Boc-L-alanine and 3-amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{24}H_{28}ClN_4O_4$ (MW = 471.18); mass spectroscopy 471

Anal. calcd for $C_{24}H_{28}ClN_4O_4$: C, 61.21; H, 5.78; N, 11.90. Found: C, 61.24; H, 5.59; N, 11.67.

Step D - Preparation of 3-(L-Alaninyl)amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-tert-butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material was used immediately.

Example 8-D

Synthesis of 3-(L-Alaninyl)amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-A using 3-(benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one (Neosystem), the title intermediate was prepared as a white foam.

$C_{24}H_{19}BrFN_3O_3$ (MW = 496.36); mass spectroscopy 497.

Anal. calcd for $C_{24}H_{19}BrFN_3O_3$: C, 58.08; H, 3.86; N, 8.47. Found: C, 57.90; H, 4.15; N, 8.20.

Step B - Preparation of 3-Amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

Step C - Preparation of 3-[N'-(*tert*-Butylcarbamate)-L-alaninyl]-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure III-D using N-Boc-L-alanine (Novo) and 3-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{24}H_{26}BrFN_4O_4$ (MW = 533.12); mass spectroscopy 533.2.

Anal. calcd for $C_{24}H_{26}BrFN_4O_4$: C, 54.04; H, 4.91; N, 10.50. Found: C, 53.75; H, 4.92; N, 10.41.

Step D - Preparation of 3-(L-Alaninyl)-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material was used immediately.

Example 8-E

Synthesis of